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Incidence of kidney toxicity of non-steroidal anti-inflammatory drugs in critically ill patients

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ABSTRACT

Background: Analgesia is paramount to improving critically ill patients recovery and preventing complications, especially during the post-operative time. Nonsteroidal anti-inflammatory drugs (NSAIDs) provide cost-effective analgesia but also carry risks, including gastrointestinal bleeding and acute kidney injury (AKI). Their safety in this setting is poorly understood.

Methods: All patients admitted to the Hospital Vila Franca de Xira ICU for more than 24 h, from January 1st 2015, to December 31st 2023, were included. Acute kidney injury was tracked throughout the ICU and hospital stay for all included patients, using the serum creatinine and urine output. Patients already with kidney dysfunction on admission to the ICU, either chronic or acute, were excluded. Short- and long-term outcomes (until 2 years of follow-up) were retrieved.

Results: The study included 1157 patients. NSAIDs were more commonly used among surgical patients (62. in non-scheduled and 61. in scheduled surgery) than medical patients (23., $p < 0.001$). Its use was associated with higher AKI rates (67. vs. 51., $p = 0.009$), including severe AKI (stage 3, 34. vs. 26., $p = 0.008$). Notably, while non-severe AKI had no significant impact on 2-year survival, severe AKI was associated with significantly worse survival (adjusted hazard ratio 1.42, confidence interval 1.09–1.86, $p = 0.011$). Recovery of renal function did not significantly decrease the long-term survival (80. vs. 78., log-rank test, $p = 0.636$).

Conclusion: In critically ill patients, the use of NSAIDs is associated with AKI and may lead to a worse prognosis.

1. Introduction

Kidney function plays a vital role in maintaining hydroelectrolytic homeostasis. Since kidney function intrinsically depends on cardiac output, the kidney is very sensitive to its decrease [1], especially when associated with venous congestion [2]. However, the diagnosis of acute kidney injury (AKI) in critically ill patients can be challenging, as it is based on elevated serum creatinine (sCr) concentration and reduced urine output, which are poorly sensitive [3].

Critical illness is often complicated by prolonged hypoperfusion and swings in cardiac output, which exacerbates the risk of AKI. Concurrent risks (critical illness, surgery and acute injury) lead to a commonly reported high incidence of AKI in the ICU, often above 50 % [4].

After surgery, the incidence of AKI may exceed 10 % [5], even in the ward. Moreover, several commonly used drugs may further jeopardize kidney function and contribute to approximately 20 % of AKI cases [6].

Postoperative pain management with NSAIDs is often recommended for the treatment of acute pain, especially during the postoperative period. This helps to improve patient recovery and prevent complications. However, it can also be associated with an increased risk of adverse effects such as gastrointestinal injury, cardiovascular morbidity and mortality, and kidney impairment [7].

We intended to evaluate the kidney safety of NSAIDs in a critically ill population.

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2. Patients and methods

This is a retrospective review of all patients admitted for more than 24 h in the Hospital Vila Franca de Xira ICU from January 1st, 2015, to December 31st, 2023. All adult patients without evidence of kidney dysfunction on admission were included. Patients were divided according to the use of NSAIDs during their ICU stay.

3. Data collection and definition

All data were collected from Hospital Vila Franca de Xira electronic databases, including the ICU informatics platform (B ICU® care), Glintt® electronic system, and Maxdata® laboratory system.

For each patient, clinical and demographic data were extracted, including sex, age, and comorbidities. Sepsis at ICU admission was registered along with the simplified acute physiology score (SAPS II) [8]. Long-term follow-up, up to two years after ICU admission, was conducted for all included patients. The patients' status (dead or alive) was recorded, including the date of death (if applicable). Mortality up to 2 years of follow-up was compared based on the type of admission and the presence of AKI.

Exclusion criteria included age below 18 years, ICU stays shorter than 24 h, AKI diagnosis on ICU admission, estimated glomerular filtration rate (eGFR), calculated with Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021 equation [9], on ICU admission equal or below 10 ml/min, previous kidney transplant, chronic treatment with renal replacement therapy and largely incomplete data files.

4. Acute kidney injury

The diagnosis of AKI was based on the KIDGO criteria, including sCr and urine output data [3]. Laboratory data were retrieved for the duration of the hospital stay to identify changes in sCr. The baseline eGFR was calculated with the CKD-EPI 2021 equation. The highest sCr measured between 24 h before ICU admission and during the first 24 h of ICU stay was selected to ensure that we exclude all AKI episodes happening before ICU admission (and therefore not related to NSAIDs use). Urine output was measured every 6 h during the whole ICU stay. Urine output per body weight was computed and used to identify AKI stages 1 to 3.

Patients were categorized according to the KDIGO criteria for AKI, stages 1 to 3 (according to the highest stage achieved during hospital stay, using both the sCr and the urine output criteria, whichever was higher), or no kidney failure.

The last measured sCr (during the hospital stay) was used to compute discharge eGFR. Patients with a discharge eGFR less than 90 % of the admission eGFR were considered to have persistent AKI.

5. Statistical analysis

Descriptive data are presented as either mean ± standard deviation or median, according to data distribution. Categorical variables were described as N (%). The chi-square test was used to compare categorical variables, while continuous variables were assessed using the Student's *t*-test, Mann-Whitney *U* test or Kruskal-Wallis test, depending on the data distribution. A logistic regression model was developed to assess the impact of NSAIDs use on severe AKI (stage 3), and a second one, including only patients medicated with NSAIDs, to identify risk factors for developing AKI among those patients. All variables with a *p*-value <0.10 in univariate analysis were included. Variables considered important for influencing the risk of AKI (such as diabetes and age) were also forced into the models.

Short- and long-term survival curves were plotted for the different groups. Comparisons were made using the Mantel-Cox test. Cox proportional hazards regression was computed for the long-term outcome, adjusting for persistent AKI, age and severity of the acute disease.

A Kaplan-Meyer survival curve was plotted for comparison of patients with or without persistent AKI discharged alive from the hospital. The log-rank test was computed.

Statistical analysis was performed using IBM SPSS Statistics v.29.0 (IBM, Somers, NY, USA). All statistical tests were two-tailed, and the significance level was set at $p < 0.05$.

6. Results

During the study period, 5063 patients were admitted to the Hospital Vila Franca de Xira ICU for more than 24 h. Of these, 1157 met the inclusion criteria, including 851 (73.6 %) medical and 306 (26.4 %) surgical admissions (166 elective and 140 urgent). NSAIDs analgesia was more common among surgical patients (61.8 % vs. 23.6 % in medical patients, $p < 0.001$).

Patients receiving NSAIDs were significantly younger, had lower severity on ICU admission (according to the SAPS II), and had a lower prevalence of diabetes and hypertension. However, NSAIDs use was associated with a higher incidence of AKI (67.2 % vs. 51.2 %, $p = 0.009$) and severe AKI (34.4 % vs. 26.7 %, $p = 0.008$) – Table 1. (See Table 2.)

The mean time until stage 3 AKI diagnosis was similar between patients receiving NSAIDs (5.2 days) or not (5.7 days). These were independent of the criteria used, either sCr or urine output.

No differences in short- and long-term mortality were observed.

This difference in the incidence of AKI was also observed in the surgical subgroup, where patients receiving NSAIDs had a higher AKI rate compared to those not exposed (43.4 % vs. 26.5 %, $p = 0.003$).

7. Acute kidney injury

According to the KDIGO criteria, severe AKI (KDIGO stage 3) was diagnosed in 339 (29.3 %) of our population, including 63 patients with both sCr and the urine output criteria. Of the remaining, sCr criteria were used to diagnose 76 patients, whilst 74 had only a urine output criteria.

In the multivariable analysis model assessing risk factors for severe AKI (KDIGO stage 3), diabetes, sepsis, and the use of NSAIDs were stronger predictors of severe AKI. Neither age, type of admission, nor eGFR on admission were independently associated with severe AKI.

Table 1
Use of NSAIDs during ICU stay.

	No ($n = 767$)	NSAIDs ($n = 390$)	P- value
Age	63.0 ± 17.9	60.4 ± 18.1	0.02**
Gender (male)	54.6 %	61.3 %	0.033*
CDK-EPI 21	51.1 ± 31.7	49.2 ± 32.6	0.344**
SAPS II	34.8 ± 16.7	31.5 ± 16.6	0.003**
Diabetes	19.8 %	9.3 %	<0.001*
Hypertension	37.7 %	24.9 %	<0.001*
Chronic Hepatic Disease	35.1 %	33.7 %	0.646*
Heart Failure	12.1 %	4.9 %	<0.001*
Neoplasic Disease	9.1 %	23.6 %	<0.001*
Sepsis	17.7 %	18.1 %	0.87*
AKI	51.2 %	67.2 %	0.009*
Severe AKI (KDIGO =3)	26.7 %	34.4 %	0.008*
KRT	9.6 %	8.5 %	0.592*
LOS (ICU)	3 [2–5]	3 [2–7]	0.007#
LOS (hospital)	8 [5–14]	10 [5–20]	<0.001#
Hospital Mortality	12.9 %	14.4 %	0.523*
1st Year Mortality	26.6 %	22.6 %	0.152*
2nd Year Mortality	32.3 %	27.7 %	0.121*

NSAIDs- Non-Steroid Anti-Inflammatory Drugs; CDK-EPI 21- Chronic Kidney Disease Epidemiology Collaboration (2021); SAPS II- Simplified Acute Physiology Score II; KDIGO- Kidney Disease: Improving Global Outcomes; KRT- Kidney Replacement Therapy; LOS- Length of Stay; ICU- Intensive Care Unit.

* Chi-square test.

** Student's *t*-test.

\# Mann Whitney *U* test.

Table 2
Risk factors for Developing Severe Acute Kidney Injury (KDIGO = 3).

	Adjusted Odds Ratio	95 % CI	P- Value
Type of Admission (NSS)			Control
Type of Admission (M)	0.54	0.33–0.89	0.015
Type of Admission (SS)	0.67	0.41–1.10	0.114
SAPS II	1.02	1.01–1.03	0.002
IMV	1.90	1.35–2.68	<0.001
NSAIDs	1.98	1.43–2.74	<0.001
Diabetes	2.62	1.76–3.89	<0.001
Chronic Hepatic Disease	1.67	1.21–2.29	0.002
Sepsis	2.12	1.50–3.00	<0.001

CI- Confidence Interval; NSS- Non-Schedule Surgery; M- Medical; SS- Schedule Surgery; SAPSII- Simplified Acute Physiology Score II; IMV- Invasive Mechanical Ventilation; NSAIDs- Non-Steroidal Anti-Inflammatory Drugs; KDIGO- Acute Kidney Injury Network classification.

At hospital discharge, 26.8 % of patients alive with AKI stage 1, 22.7 % of AKI stage 2, and 29.5 % of AKI stage 3, had persistent AKI. A Kaplan-Meyer survival curve was plotted comparing patients with or without persistent AKI (Fig. 1). No significant differences were noted.

The relationship between KDIGO stages and 2-year survival is presented in Fig. 2, showing no impact on mortality for AKI stages 1 and 2, while AKI stage 3 is associated with significantly higher short- and long-term mortality (Log-Rank test $p < 0.001$).

In a Cox proportional hazard evaluation, age, SAPS II, IMV, metastatic oncological disease, haemato-oncological disease and KDIGO stage 3 (but not stages 1 and 2), all prove to be independent predictors of 2-year mortality (Table 3).

8. Discussion

The study provides significant insights into the relationship between NSAIDs use, AKI risk and staging, and clinical outcomes in critically ill patients.

We evaluated 1157 patients admitted to the Hospital Vila Franca de Xira ICU for more than 24 h, of whom 26.4 % were postoperative (with roughly half undergoing non-scheduled surgery). One-third of the whole population received NSAIDs for at least 24 h during their ICU stay, particularly the post-operative population. Although we excluded patients with AKI on admission, we found that a further 40 % of our population developed AKI during their hospital stay (according to the KDIGO criteria).

Despite being younger and less severely ill, patients treated with NSAIDs were significantly more likely to develop AKI (67.2 % vs. 51.2 %, $p = 0.009$) and severe AKI (34.4 % vs. 26.7 %, $p = 0.008$). Similar findings were observed in the surgical subgroup. The higher incidence of severe AKI in the population receiving NSAIDs remained significant after adjusting for confounding variables (adjusted OR 1.98, 95 % CI 1.43–2.74, $p < 0.001$).

This is particularly important because severe AKI acquired after ICU admission, whether in the ICU or on the ward, is associated with worse short- and long-term outcomes, up to two years after ICU admission, even in patients who appear to recover kidney function before hospital discharge [10]. A steady decline in eGFR during recovery from the critically ill disease [11] may contribute to a worse long-term prognosis, although, in this study, AKI stages 1 and 2 had no impact on long-term mortality. In our study, recovery of renal function before hospital discharge had no significant impact on 2-year all-cause mortality.

The widespread use of NSAIDs in the ICU reflects their utility in pain management, particularly postoperative, given their opioid-sparing effects, affordability, and benefits in recovery [12]. However, their use must be carefully balanced against the risk of AKI, especially in these critically ill patients. In an era of concern over the widespread adverse effects of opioids, especially dependence, these data are critical to properly balance the benefits with the risks.

One of the most striking findings of our study was the strong association between NSAIDs use and the development of KDIGO Stage 3 (incidence: 34.4 % vs. 26.7 % adjusted OR 1.98, 95 % CI 1.43–2.74, $p < 0.001$). This suggests that NSAIDs, widely used for pain management in ICU patients, may contribute to the progression of AKI in at-risk populations.

This association was not found by Chang et al. in the early post-operative period following major gastrointestinal surgery. However, our study assessed AKI during the whole hospital stay and used both SCr and urine output criteria, as previously recommended [13], thereby strengthening our findings. Establishing a “security threshold” for NSAIDs would be advantageous, as these medications are highly effective for pain relief. Also, the relationship between baseline renal

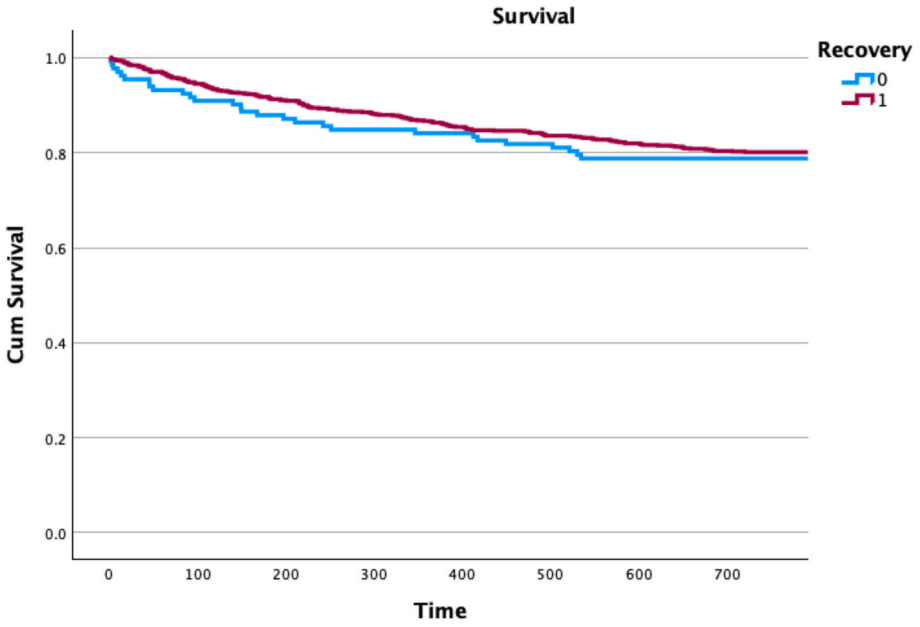

Fig. 1. Long-term survival and recovery of Acute Kidney Injury. Two-year Kaplan-Meyer survival curve of patients discharged alive from the hospital according to recovery of renal function before discharge. Log-Rank test $p = 0.636$.

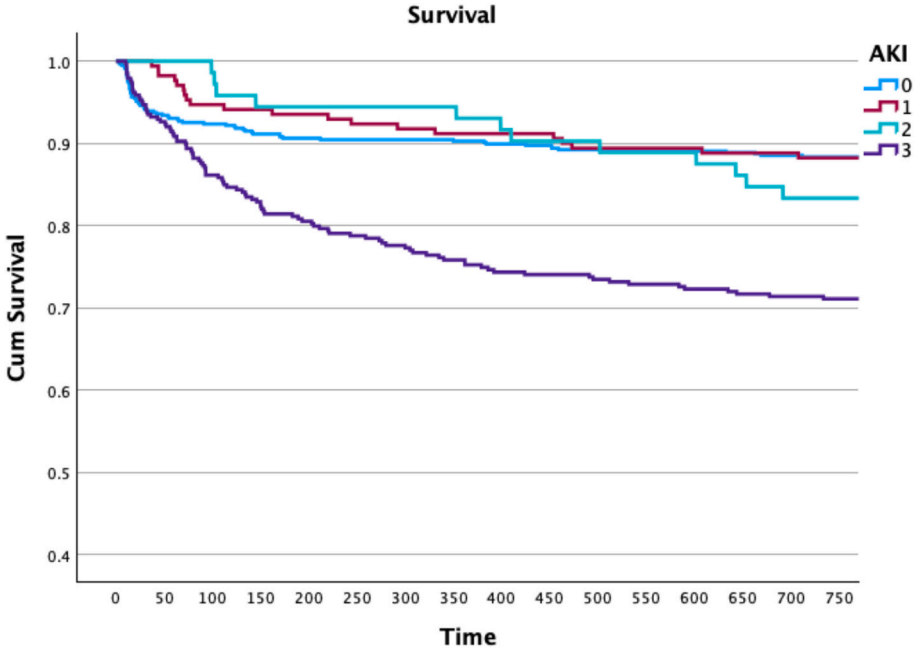

Fig. 2. Long Term survival and Acute Kidney Injury. Two-year Kaplan-Meyer Survival curve according to the stage of acute kidney injury (AKI; none, 1, 2, 3). Log-Rank test $p < 0.001$. AKI stages 1 and 2 have no impact on mortality.

Table 3
Risk factors for 2-year all-cause mortality.

	Adjusted hazard ratio	95 % CI	*P*-value
SAPS II	1.03	1.03–1.04	<0.001
Age	1.02	1.02–1.03	<0.001
IMV	1.43	1.11–1.85	0.006
Metastatic Disease	3.09	2.07–4.61	<0.001
Haemato-oncological Disease	3.05	1.73–5.38	<0.001
No AKI			Control
AKI (stage 1)	0.80	0.56–1.14	0.219
AKI (stage 2)	1.10	0.70–1.72	0.685
AKI (stage 3)	1.42	1.09–1.86	0.011

CI- Confidence Interval; SAPSII- Simplified Acute Physiology Score II; IMV- Invasive Mechanical Ventilation; AKI- Acute Kidney Injury.

function, coexistence of heart or hepatic disease, acute bleeding or other high-risk groups, should be addressed in future studies of NSAIDs use.

Our study has several limitations: First, its retrospective nature increases the potential for selection bias and incomplete data. Additionally, doctors using NSAIDs for pain control were likely to avoid these drugs in patients perceived to be at high risk for AKI (e.g. elderly patients), which may have influenced our results. Second, we were only able to collect information about urine output during the ICU stay, although isolated urine output changes are often observed during the early days after the insult. Third, the restrictive exclusion criteria may limit the generalizability of our findings. Furthermore, as a single-center study, its applicability to broader ICU populations may be limited and confirmatory studies are needed. Fourth, the design of our study did not enable us to account for unmeasured factors, such as dosing, timing or cumulative exposure to NSAIDs. This is even more striking, as several patients received NSAIDs "on demand", and measurement of exposure is limited. We also did not measure exposure to other nephrotoxic drugs, especially during the ward stay. Fifth, bleeding or other complications before ICU admission (or even after discharge) were not assessed and might have influenced our results.

This study also has some strength: Our restrictive inclusion criteria allow us to have a homogeneous population, to better study NSAIDs toxicity. Moreover, including ward laboratory data in the study helped us to identify several patients who developed AKI in the hospital, even after ICU discharge. Finally, the inclusion of 2-year mortality data provides a comprehensive perspective on patient outcomes beyond the hospital stay.

Our findings highlight the importance of cautious NSAIDs use and vigilant monitoring of kidney function in critically ill patients. Future research should explore preventive strategies, including individualized fluid management protocols and the optimized perioperative care, as well as alternative analgesic strategies to mitigate the risk of AKI.

9. Conclusion

AKI is common in critically ill patients. The use of NSAIDs for pain control was independently associated with higher rates of AKI, including severe AKI (KDIGO stage 3). Sepsis, SAPS II and the need for IMV were also associated with severe AKI, whilst neither age nor baseline kidney function were.

Severe AKI, acquired after ICU admission, either in the ICU or in the ward, was associated with worse short- and long-term mortality, while KDIGO stages 1 and 2 had no impact on mortality in this cohort.

CRediT authorship contribution statement

Carolina Gomes: Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Conceptualization. **Maria Inês Proença Pereira:** Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Patrícia Valério:** Visualization, Methodology, Investigation, Formal analysis. **João Barbosa Barroso:** Resources, Methodology, Investigation, Formal analysis. **Tânia Mendes:** Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **João Gonçalves Pereira:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

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